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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,347	11/09/1999	CHRISTINE A. WHITE	012712-643	6491

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EXAMINER	
HARRIS, ALANA M	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 07/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/436,347	WHITE ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-11,13,14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-11, 13, 14 and 16-18/* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments and Arguments

1. Claims 4-11, 13, 14 and 16-18 are pending.

Claims 4, 5 and 7-10 have been amended.

Claims 1-3, 12 and 15 have been cancelled.

Claims 4-11, 13, 14 and 16-18 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

New Grounds of Objection

Specification

3. In light of Applicants' amendment to the specification to include the proper recitation of the trademark, RITUXAN® (rutximab) the objection is withdrawn.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

4. The new matter rejection of claims 4-11, 13, 14 and 16-18 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of Applicants' cancellation of claims 1 and 12 and the amendment of claim 14. Claims 1-3, 12 and 15 have been cancelled.

5. The rejection of claims 4-11, 13, 14, 16 and 17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn. Claims 1-3, 12 and 15 have been cancelled.

Claim Rejections - 35 USC § 102

6. The rejection of claims 4, 6, 7, 9 and 13, 14, 16 and 17 under 35 U.S.C. 102(a) as being anticipated by McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2004) is withdrawn in light of Applicants' arguments. Claims 1-3, 12 and 15 have been cancelled.

Claim Rejections - 35 USC § 103

7. The rejection of claims 4-11, 13, 14 and 16-18 under 35 U.S.C. 103(a) as being unpatentable over McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS reference B1, submitted October 19, 2004), in view of U.S. Patent number 6,682,734 (effective filing date November 13, 1992) and EP document 0 510 949 A2 (April 23, 1991) is withdrawn in light of Applicants' arguments. Claims 1-3, 12 and 15 have been cancelled.

Maintained and New Grounds of Rejection

Claim Rejections - 35 USC § 102

8. The rejection of claims 4, 5, 8, 11, 13, 14, 16 and 28 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,090,365 (field November 18, 1997) is maintained and made. Applicants argue "the Kaminski patent does not anticipate claim 13" and "...does not teach treatment of B-PLL, CLL or transformed non-Hodgkin's lymphoma with an antibody that binds the CD20 antigen, or fragment thereof as set forth in claim 13.", see bridging paragraph of pages 13 and 14 of the Remarks submitted May 2, 2005 and first full sentence on page 14. The amendment to claim 13 submitted on May 2, 2005 and these points of view have been carefully considered but found unpersuasive.

U.S. Patent #6,090,365 discloses methods for treatment of chronic lymphocytic leukemia (CLL), chronic myeloblastic leukemia and lymphomas by administration of a B-cell specific antibody, antibody B1, see the abstract; column 5, lines 25-35; column 7, lines 24-47; and column 13, lines 40-61. This antibody is regarded as a CD-20 antibody based on the patent's disclosure of "B1 anti-CD20", as well as the fact the B1 antigen is also referred to as CD20, see column 8, lines 12-15 and 48-50. Logically it seems clear an alternate name for the B1 antibody is a CD20 antibody. The disclosed method sets forth the concurrent treatments of an antibody or antibody fragment that binds to the CD20 antigen and the administration of a radioisotope conjugated to said antibodies or a chemotherapeutic agent, see column 35, lines 12-20; column 38, claim 11 and column 39, claim 14.

Applicants' inference that B1 binds antigens other than CD19 and CD20 does not preclude the B1 antibody from being recognized as a CD20 antibody specifically bind the CD20 antigen, nor does this point of view teach away from the administration of an antibody that binds to the CD20 antigen on human B cells. The patent discloses dose escalation of ^{90}Y labeled B1 can be performed in a cautious progression which reads on Applicants' limitation of a stepped-up dosage scheme, see column 23, lines 38-40. Inherent in the disclosed method of administering an antibody that binds to the CD20 antigen is the simultaneous implementation of methods of avoiding or reducing toxicity and reduction in circulating tumor cells.

It is reasonable to conclude that B-prolymphocytic leukemia (B-PLL) and transformed non-Hodgkin's lymphoma would also be treated using the disclosed methodology to achieve the reduction in circulating tumor cells in light of the patent's disclosure of the successful treatment of the listed leukemias and lymphomas.

The patent discloses the use of antibodies comprising the B1 antigen-binding domain, as well as alternative method of "humanization "of the antibody and Fab, Fab', or $F(ab')_2$ fragments administered in a range from 0.2 to 40mg/kg, which reads on Applicants' range, see column 7, line 57- column 8, line 11 and column 10, lines 62-64.

Claim Rejections - 35 USC § 103

9. Claims 4, 5, 8, 11, 13, 14, 16 and 28 under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent number 6,090,365 (field November 18, 1997), in view of McLaughlin et al. (Journal of Clinical Oncology 16(8): 2825-2833, August 1998/ IDS

reference B1, submitted October 19, 2004), U.S. Patent number 6,682,734 (effective filing date November 13, 1992) and EP document 0 510 949 A2 (April 23, 1991). The teachings of U.S. patent #6,090,365 were presented in the 102(e) rejection. The patent does not teach the claimed method, wherein the antibody is explicitly rituximab, administered weekly for about 2 to 10 weeks, at a dosage of a 375mg/m^2 weekly for a total of four weeks, particularly administered at an initial dose of 100mg/m^2 and the remainder of a 375mg/m^2 is administered on the following day. Patent '365 also does not teach the method inclusive of an additional treatment such as lymphokine administration.

However, McLaughlin teaches a method of treating patients with several types of lymphoma with the administration of a chimeric anti-CD20 monoclonal antibody, rituximab (IDEC-C2B8), see title and Patients and Methods section on page 2826, column 1. All of the patients were given an antibody dose of 375mg/m^2 intravenously once weekly for a total of four infusions, see abstract and page 2826, column 1, Therapy section. "The initial infusion rate was 50mg/h, with subsequent infusion rate increase...", see cited Therapy section.

Secondly, U.S. patent #6,682,734 teaches the administration of effective dosages or therapeutically effective amounts of immunologically active chimeric anti-CD20 antibodies from about 0.001 to about 30 mg/kg body weight and suggests that the skilled artisan could easily assess a suitable dosage for a particular patient, see column 7, lines 16-26. Moreover, EP 0 510 949 A2 teaches conjugate moieties comprising antibodies and interleukins 1-10, GM-CSF, TNF and interferons and their subsequent

administration for treatment of leukemias and lymphomas, see column 3, lines 27-47; column 5, lines 23-31; bridging paragraph of columns 5 and 6.

It would have been *prima facie* to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of both patents, McLaughlin and the EP document in order to efficaciously treat cancer. One of ordinary skill in the art would have been motivated to combine the teachings of all the documents with a reasonable expectation of success because McLaughlin cites there has been "...evidence of synergism between [rituxumab] and some chemotherapeutic agents", see page 2831, column 2, last paragraph before Acknowledgment section. Moreover, McLaughlin establishes the successful treatment of different B-cell lymphomas thereby motivated one of ordinary skill in the art to implement a method of rituximab administration to other B-cell malignancies expressing CD20 antigen, see abstract and bridging paragraph of pages 2825 and 2826. It is art known that toxins have been conjugated to antibodies, as well as a variety of radionuclides for targeted immunotherapy, and the conjugates may be used to specifically destroy cells associated with a pathogenic condition (i.e. leukemias and lymphomas), see patent '734, column 3, lines 55-58 and column 8, line 11-column 9, line 22; and EP document, abstract and column 5, lines 23-31.

Furthermore, it is clear in the 6,090,365 patent that methods of therapeutic treatment of lymphomas with B cell-specific antibody is well recognized in the art. It would have been *prima facie* to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings of the primary reference, '395 patent with

the remaining references in order to administer therapeutic antibodies that recognize the CD20 antigen, which is expressed on more than 90% of B-cell lymphomas to patients for cancer treatment. One of ordinary skill in the art would have been motivated to combine the teachings of all the documents with a reasonable expectation of success because each reference discusses alternative therapeutic strategies and non-limiting approaches to successful leukemia and lymphoma cancer treatment.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571)272-0831. The examiner works a flexible schedule, however she can normally be reached between 6:30 am to 5:30 pm with alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ALANA M. HARRIS, PH.D.
PRIMARY EXAMINER

Alana M. Harris, Ph.D.
05 July 2005